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BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte SHIRLEY LONGACRE-ANDRE, CHARLES ROTH, FARIDABANO NATO, JOHN W. BARNWELL, and KAMINI MENDIS

Appeal 2011-003158
Application 09/134,333
Technology Center 1600

Before DEMETRA J. MILLS, MELANIE L. McCOLLUM, and JEFFREY N. FREDMAN, Administrative Patent Judges.

FREDMAN, Administrative Patent Judge.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 involving claims to a vaccinating composition. The Examiner rejected the claims as obvious. We have jurisdiction under 35 U.S.C. § 6(b). We affirm.

Statement of the Case

Background

"MSP-1 has already been the subject of a number of studies. It is synthesized in the schizont stage of Plasmodium type parasites . . . and is expressed in the form of one of the major surface constituents of merozoites both in the hepatic stage and in the erythrocytic stage of malaria" (Spec. 1, ll. 6-10). The Specification teaches that because MSP-1's "predominant character and conservation in all known Plasmodium species, it has been suggested that it could be a candidate for constituting anti-malarial vaccines" (Spec. 1, ll. 10-13).

The Claims

Claims 134, 139-142, 145, 148-155, 157, 158, 160, 161, 163, 164, and 166-177 are on appeal. Claims 151 and 153 are representative and read as follows:

> 151. A recombinant protein whose polypeptide sequence comprises:
>
> a) a leader sequence comprising thirty-two amino acids of a surface protein 1 of a merozoite form (a MSP-1 protein) of Plasmodium vivax from Met_1 to ASP_{32}; and
>
> b) a 19 kilodalton C-terminal fragment of a surface protein 1 of a merozoite form (a MSP-1 protein) of Plasmodium falciparum consisting of an amino acid sequence from Asn at amino acid position 3 to Ser at amino acid position 95 of SEQ ID NO: 1 which fragment induces an immune response which can inhibit parasitemia in vivo in a host infected with a Plasmodium parasite.

153. A recombinant protein whose polypeptide sequence consists of:

a) a leader sequence comprising thirty-two amino acids of a surface protein 1 of a merozoite form (a MSP-1 protein) of Plasmodium vivax from Met_1 to Asp_{32}; and

b) a 19 kilodalton C-terminal fragment of a surface protein 1 of a merozoite form (a MSP-1 protein) of Plasmodium cynomolgi consisting of an amino acid sequence from Lys_{276} to Ser_{380} as shown in SEQ ID NO: 11 which fragment induces an immune response which can inhibit parasitemia in vivo in a host infected with a Plasmodium parasite, and wherein the fragment has atomic coordinates in AnnexI; and NMR fingerprints of Figures 12.0a to 12.0c.

The issues

A. The Examiner rejected claims 153, 169, 172, and 175 under 35 U.S.C. § 103(a) as obvious over Longacre (1995)[1] and Longacre (1994)[2] (Ans. 4-7).

B. The Examiner rejected claims 151, 152, 154, 155, 157, 158, 160, 161, 163, 164, 166, 167, 168, 170, 171, 173, and 174 under 35 U.S.C. § 103(a) as obvious over Longacre (1995), Longacre (1994), Chappel,[3] and Miller[4]

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[1] Longacre, Shirley, The Plasmodium cynomolgi merozoite surface protein 1 C-terminal sequence and its homologies with other Plasmodium species, 74 MOLECULAR BIOCHEMICAL PARASITOLOGY 105-111 (1995), hereinafter "Longacre (1995)".

[2] Longacre et al., Plasmodium vivax merozoite surface protein 1 C-terminal recombinant proteins in baculovirus, 64 MOLECULAR BIOCHEMICAL PARASITOLOGY 191-205 (1994), hereinafter "Longacre (1994)".

[3] Chappel et al., Monoclonal antibodies that inhibit Plasmodium falciparum invasion in vitro recognise the first growth factor-like

(Ans. 8-10).

C. The Examiner rejected claims 134, 139-141, 145, 148-150, 176, and 177 under 35 U.S.C. § 103(a) as obvious over Longacre (1995), Longacre (1994), and Holder (Ans. 10-11).

D. The Examiner rejected claims 134, 139-142, 148, 150, 176, and 177 under 35 U.S.C. § 103(a) as obvious over Chappel, Miller, Longacre (1995), Longacre (1994), and Holder[5] (Ans. 10-11).

A. 35 U.S.C. § 103(a) over Longacre (1995) and Longacre (1994)

The Examiner finds that Longacre (1995) "teaches the cloning of the Plasmodium cynomolgi C-terminal merozoite surface protein (MSP-l) sequence in the $pVLSV_{200}$ plasmid . . . a plasmid containing the N-terminal signal sequence of the MSP-l protein of Plasmodium vivax, containing residues Met_1-Asp_{32}" (Ans. 5). The Examiner finds that Longacre (1995) "suggests the use of the C-terminal MSP-l polypeptide fragments for vaccine studies" (Ans. 5). The Examiner finds that Longacre (1994) teaches "the C-terminal p42 and p19 fragments of MSP-l proteins as notoriously old and well known vaccine candidates in the art" (Ans. 5). The Examiner finds that Longacre (1994) "demonstrates that baculovirus constructs containing an appropriate MSP-1 signal sequence can be used for the expression of various

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domain of merozoite surface protein-1, 60 MOLECULAR BIOCHEMICAL PARASITOLOGY 303-311 (1993).

[4] Miller et al., Analysis of sequence diversity in the Plasmodium falciparum merozoite surface protein-1 (MSP-1), 59 MOLECULAR BIOCHEMICAL PARASITOLOGY 1-14 (1993).

[5] Holder et al., US 5,720,959, issued Feb. 24, 1998.

length soluble or anchored C-terminal fragments of the MSP-1 protein with tertiary structures resembling the native protein for vaccine studies" (Ans. 6).

> The Examiner finds it obvious
>
> to have used the plasmid transfer vector and a baculovirus construct containing the encoded cloned Plasmodium cynomolgi C-terminal MSP-1 protein sequence . . . as taught in [Longacre (1994)], in [Longacre (1995)] for the production and isolation of encoded C-terminal MSP-1 protein region or fragments because [Longacre (1995)] desires the Plasmodium cynomolgi C-terminal MSP-1 protein region or fragments thereof for vaccine studies and [Longacre (1994)] teach that such similar constructs had been successfully used for protein production and isolation of the homologous fragments from a number of other species of malarial parasites for such studies.

(Ans. 6-7).

Appellants contend that Longacre (1995) "does not disclose that the amino acid sequence from Lys_{296} to Ser_{380} as shown in SEQ ID NO: 11 induces an immune response which can inhibit parasitemia in vivo in a host infected with a Plasmodium parasite" (App. Br. 8). Appellants contend that Longacre (1994) "does not disclose or suggest that the recombinant constructs produced therein can induce an immune response, which can inhibit parasitemia in vivo in a host infected with a Plasmodium parasite" (App. Br. 8).

Appellants contend that Arnot[6] demonstrates unexpected results using baculovirus $MSP1_{19}$, since "Baculovirus produced $MSP\text{-}1_{19}$ immunizations produce the highest parasite-specific antibody titers in immunofluorescence assays; induced more antibodies, in ELISAs, gave the highest levels of growth inhibitor in HB3 and 3D7 parasite cultures and inhibited growth as well as or better at lower IgG concentrations." (App. Br. 8). Appellants contend that "due to the unpredictability in this art the mere production of recombinant proteins and oligomers thereof cannot be equated with their physiologic action in vivo unless truly demonstrated" (App. Br. 9).

The issues with respect to this rejection are:

(i) Does the evidence of record support the Examiner's conclusion that Longacre (1995) and Longacre (1994) render obvious the method of claim 153?

(ii) If so, have Appellants presented evidence of secondary considerations, that when weighed with the evidence of obviousness, are sufficient to support a conclusion of non-obviousness?

Findings of Fact

1. The Specification teaches that the "recombinant construction $PcMSP1_{p19}S$ contains the DNA corresponding to 8 base pairs of the leader sequence and the first 32 amino acids of the MSP-1 of Plasmodium vivax from Met_1 to Asp_{32}" (Spec. 22, ll. 7-9).

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[6] Arnot et al., Comparative Testing of Six Antigen-Based Malaria Vaccine Candidates Directed Toward Merozoite-Stage Plasmodium falciparum, 15 CLINICAL VACCINE IMMUNOLOGY 1345-1355 (2008).

2. The Specification teaches that the leader is followed by GluPhe which "is followed by the sequence coding for the Plasmodium cynomolgi $MSP1_{p19}$ from Lys_{276} to Ser_{380}" (Spec. 22, ll. 10-13).

3. Longacre (1994) teaches that in "the first step, DNA corresponding to 8 bp of leader sequence and the N-terminal 33 amino acids of pV200 (including the signal sequence) was generated by the polymerase chain reaction from pV200" (Longacre (1994) 192, col. 2).

4. Figure 2 of Longacre (1994) is reproduced below:

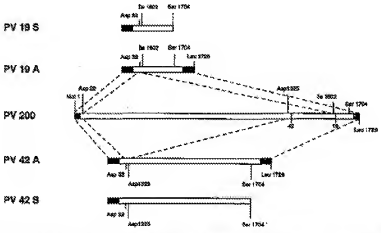

Fig. 2. Diagram of the baculovirus constructs derived from the *P. vivax* MSP1 gene. The pV200 sequence was that determined from the Belem strain of *P. vivax* by *etal* Portillo et al. [27]. Black boxes indicate the pV200 signal sequence; gray shading indicates the pV200 transmembrane region. Vertical lines indicate the hypothetical cleavage sites which presumably generate the *P. vivax* 42-kDa and 19-kDa processing analogs.

Figure 2 shows a diagram of baculovirus constructs derived from the P. vivax MSP1 gene, with a signal sequence comprising Met_1 to Asp_{32}.

5. Longacre (1994) teaches that a "comparison of the P. vivax and P. falciparum MSP1 sequences (as well as those from other species) shows that the C-terminal portion corresponding to the 19-kDa fragment is one of the most conserved regions" (Longacre (1994) 202, col. 2).

6. Longacre (1994) teaches that the "baculovirus constructs used in the work presented here were designed to produce P. vivax MSP1 C-

terminal proteins closely analogous to the native processed fragments" (Longacre (1994) 201, col. 1).

7. Longacre (1994) teaches that "[s]ince we were able to obtain efficient secretion of our recombinants in a low-protein, serum-free medium, it was possible to obtain substantially enriched (80-90% pure in some cases) preparations of recombinant protein simply by harvesting and concentrating culture supernatants" (Longacre (1994) 202, col. 1).

8. Longacre (1995) teaches that a "prominent molecular vaccine target for malaria is the merozoite surface protein 1 . . . This 200-kDa molecule is processed in two steps, giving rise to a glycosylphosphatidylinositol-anchored C-terminal 42-kDa moiety which is further cleaved to a 19-kDa species" (Longacre (1995) 105-106).

9. Longacre (1995) teaches that the "19-kDa fragment is retained by the merozoite during invasion and is rich in highly conserved cysteines that are proposed to form two epidermal growth factor (EGF)-like domains. A number of studies have substantiated the potential of MSP-1 and particularly its C-terminal polypeptides as possible vaccine candidates" (Longacre (1995) 106, col. 1; refs. omitted).

10. Longacre (1995) teaches an "interest of P. cynomolgi as a highly relevant model for testing the potential of MSP-1 as a vaccine candidate" (Longacre (1995) 109, col. 2).

11. Longacre (1995) teaches that as

> a first step towards using the macaque and P. cynomolgi as a natural host:parasite system to test the potential of the C-terminal region of MSP-1 as a vaccine for P. vivax malaria, we have cloned and sequenced the corresponding portion of the P. cynomolgi ceylonesis MSP-1 gene and compared its

> primary structure with the same regions of MSP-1 from other Plasmodium species.

(Longacre (1995) 106-107).

Principles of Law

"The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." KSR *Int'l Co. v. Teleflex Inc.,* 550 U.S. 398, 416 (2007).

Analysis

Longacre (1994) teaches a baculovirus expression vector for producing the MSP-1 19kD C-terminal protein with the 32 amino acid leader sequence (FF 3-5). Longacre (1994) teaches that the "baculovirus constructs used in the work presented here were designed to produce P. vivax MSP1 C-terminal proteins closely analogous to the native processed fragments" (Longacre (1994) 201, col. 1; FF 6). Longacre (1994) teaches that "[s]ince we were able to obtain efficient secretion of our recombinants in a low-protein, serum-free medium, it was possible to obtain substantially enriched (80-90% pure in some cases) preparations of recombinant protein simply by harvesting and concentrating culture supernatants" (Longacre (1994) 202, col. 1; FF 7).

Longacre (1995) teaches an "interest of P. cynomolgi as a highly relevant model for testing the potential of MSP-1 as a vaccine candidate" (Longacre (1995) 109, col. 2; FF 10). Longacre (1995) particularly focuses on the 19 kD fragment of the MSP-1 protein as a vaccine target, noting that

a "number of studies have substantiated the potential of MSP-1 and particularly its C-terminal polypeptides as possible vaccine candidates" (Longacre (1995) 106, col. 1; FF 9).

Applying the KSR standard of obviousness to the findings of fact, we conclude that an ordinary artisan would have reasonably found it obvious to express the P. cynomolgi 19 kD C-terminal MSP-1 fragment of Longacre (1995) in the baculovirus expression system of Longacre (1994), since both papers are interested in using 19 kD C-terminal MSP-1 fragments for the generation of malaria vaccines (FF 8-10). The ordinary artisan would have chosen the baculovirus system for its native processing (FF 6) and high level of expression (FF 7). Such a combination is merely a "predictable use of prior art elements according to their established functions." KSR, 550 U.S. at 417.

Appellants contend that Longacre (1995) "does not disclose that the amino acid sequence from Lys_{296} to Ser_{380} as shown in SEQ ID NO: 11 induces an immune response which can inhibit parasitemia in vivo in a host infected with a Plasmodium parasite" (App. Br. 8). Appellants contend that Longacre (1994) "does not disclose or suggest that the recombinant constructs produced therein can induce an immune response, which can inhibit parasitemia in vivo in a host infected with a Plasmodium parasite" (App. Br. 8).

We are not persuaded. Appellants are not disputing that Longacre (1995) suggests incorporation of the amino acid sequence of from Lys_{296} to Ser_{380} as shown in SEQ ID NO: 11, which is the sequence of the MSP-1 19 kD C-terminal peptide, into a baculovirus expression vector (see FF 8-11).

Instead, Appellants are arguing that Longacre (1995) does not teach the inherent result of inhibiting parasitemia in vivo in an infected host (see App. Br. 8).

However, Longacre (1995) teaches an "interest of P. cynomolgi as a highly relevant model for testing the potential of MSP-1 as a vaccine candidate" (Longacre (1995) 109, col. 2; FF 10). In order for MSP-1 to function as a vaccine, it would necessarily require induction of an immune response which could inhibit parasitemia in vivo in an infected host. Consequently, the suggestion by Longacre (1995) that the MSP-1 sequence is a vaccine candidate does suggest inhibition of parasitemia in vivo in an infected host.

In addition, whether Longacre (1995) or Longacre (1994) appreciated that the vaccinating composition would have inhibited parasitemia in vivo does not control the obviousness inquiry. There are specific reasons given by the prior art to form the composition as discussed above (FF 3-11). "It matters not that those of ordinary skill heretofore may not have recognized these inherent characteristics." In re Cruciferous Sprout Litigation, 301 F.3d 1343, 1350 (Fed. Cir. 2002). Al*so see, e.g., MEHL/Biophile Int'*l Corp. v. Milgraum, 192 F.3d 1362, 1365 (Fed. Cir. 1999) ("Under the principles of inherency, if the prior art necessarily functions in accordance with, or includes, the claimed limitations, it anticipates.")

The burden of demonstrating that the combination of Longacre (1995) and Longacre (1994) would not inherently result in a vaccinating composition which inhibits parasitemia in vivo in an infected host rests with Appellants. See In re Best, 562 F.2d 1252, 1255 (CCPA 1977) ("Where, as

here, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product.… Whether the rejection is based on 'inherency' under 35 U.S.C. § 102, on 'prima facie obviousness' under 35 U.S.C. § 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products".)

Unexpected results

Appellants contend that Arnot demonstrates unexpected results using baculovirus $MSP1_{19}$, since "Baculovirus produced $MSP\text{-}1_{19}$ immunizations produce the highest parasite-specific antibody titers in immunofluorescence assays; induced more antibodies, in ELISAs, gave the highest levels of growth inhibitor in HB3 and 3D7 parasite cultures and inhibited growth as well as or better at lower IgG concentrations." (App. Br. 8). Appellants contend that "due to the unpredictability in this art the mere production of recombinant proteins and oligomers thereof cannot be equated with their physiologic action in vivo unless truly demonstrated" (App. Br. 9).

We are not persuaded. Arnot, published in 2008, does not demonstrate a comparison with the closest prior art of either Longacre (1994) or Longacre (1995). That is, while Arnot's selected candidate is MSP-1 sequence from Plasmodium falciparum, the comparison sequences were all from Pichia pastoris (see Arnot, abstract; "The antigens compared were recombinant baculovirus $MSP\text{-}1_{19}$ and five Pichia pastoris

candidates") However, the instant claims are directed towards baculovirus constructs with Plasmodium MSP-1 C-terminal 19 kD protein sequences, particularly from either Plasmodium cynomolgi (see, e.g., Claim 153) or Plasmodium falciparum (see, e.g., Claim 152). The prior art of Longacre (1995) suggests the use of Plasmodium cynomolgi sequence, while Longacre (1994) suggests the use of Plasmodium falciparum sequence, both of which are clearly much closer to the claims than the Pichia sequences used in Arnot. See In re Baxter Travenol Labs., 952 F.2d 388, 392 (Fed. Cir. 1991) ("[W]hen unexpected results are used as evidence of nonobviousness, the results must be shown to be unexpected compared with the closest prior art.").

Conclusions of Law

The evidence of record supports the Examiner's conclusion that Longacre (1995) and Longacre (1994) render obvious the method of claim 153. Appellants have not presented evidence of secondary considerations, that when weighed with the evidence of obviousness, are sufficient to support a conclusion of non-obviousness.

B. 35 U.S.C. § 103(a) over Longacre (1995), Longacre (1994), Chappel, and Miller

The Examiner finds that Chappel teaches "a recombinant baculovirus, similar in construction to that as instantly disclosed, i.e. having the amino terminal 34 amino acids of the P. falciparum merozoite surface protein (MSP-l) fused to 271 amino acid residues of the p42 fragment of the protein ending at residue 1723 of the sequence as disclosed and numbered in Miller" (Ans. 8). The Examiner finds it would have been obvious to "have

constructed a recombinant baculovirus expressing at least the first EGF-like domain of the C-terminal p19 fragment of the P. falciparum MSP-l protein using any of the genus of nucleotide sequences encoding the relevant amino acid sequence (Chappel et al. in view of Miller et al.) with well known methods" (Ans. 9). The Examiner finds it would have been obvious "to clone and produce the C-terminal p42 and p19 fragments of MSP-l proteins because as clearly taught by the references these fragments were notoriously old and well known vaccine candidates in the art" (Ans. 9).

Appellants contend that there "is no suggestion in Chappel and Holder to use another leader sequence from a different Plasmodium species or to limit this leader sequence to 32 amino acids. Nor is there any suggestion in this reference to construct a recombinant C-terminal MSP-l protein that has less than 271 amino acids" (App. Br. 11). Appellants contend that "Chappel and Holder fail to suggest that their recombinant proteins recited therein have the ability to induce an immune response which can inhibit parasitemia in vivo in a host infected with a Plasmodium parasite. At best their conclusion of their study was speculative" (App. Br. 12).

Appellants also contend that Arnot describes that "unexpected results of enhanced parasite-specific antibody titers, a larger induction of antibodies and higher levels of growth inhibition were achieved with baculovirus produced MSP-1_{19}" (App. Br. 13).

The issues with respect to this rejection are:

(i) Does the evidence of record support the Examiner's conclusion that Chappel, Miller, Longacre (1995) and Longacre (1994) render obvious the method of claim 151?

(ii) If so, have Appellants presented evidence of secondary considerations, that when weighed with the evidence of obviousness, are sufficient to support a conclusion of non-obviousness?

Findings of Fact

12. Chappel teaches that "$MSP1_{19}$ is composed of 2 epidermal growth factor-like motifs; we show here that the first of these growth factor-like domains is a target of invasion-inhibiting antibodies" (Chappel 303, col. 2).

13. Chappel teaches that "the first EGF-like domain in P. falciparum MSP1 is a target for antibodies capable of inhibiting parasite invasion in vitro" (Chappel 308, col. 2).

14. Miller teaches that "[i]mmunization with the first identified Plasmodium falciparum merozoite surface protein (MSP-l) protected monkeys from an otherwise fatal infection" (Miller, abstract).

15. Miller teaches that "[r]abbit antisera to a recombinant protein from the C-terminus of MSP-1 which include 294 amino acids of the dimorphic region and the highly conserved cysteine-rich block 17 blocked invasion of parasites of homologous and heterologous dimorphic types" (Miller 11, col. 1).

16. Longacre (1994) teaches that the "constructions were designed to have the P. vivax MSP1 signal sequence which would be necessary both for secretion and membrane expression" (Longacre (1994) 194, col. 2).

Analysis

Chappel teaches that "the first EGF-like domain in P. falciparum MSP1 is a target for antibodies capable of inhibiting parasite invasion in

vitro" (Chappel 308, col. 2; FF 13). Miller teaches that "[i]mmunization with the first identified Plasmodium falciparum merozoite surface protein (MSP-l) protected monkeys from an otherwise fatal infection" (Miller, abstract; FF 14).). Longacre (1995) particularly focuses on the 19 kD fragment of the MSP-1 protein as a vaccine target, noting that a "number of studies have substantiated the potential of MSP-1 and particularly its C-terminal polypeptides as possible vaccine candidates" (Longacre (1995) 106, col. 1; FF 9).

Applying the KSR standard of obviousness to the findings of fact, we conclude that an ordinary artisan would have reasonably found it obvious to express the P. falciparum 19 kD C-terminal MSP-1 fragment of Longacre Chappel and Miller in the baculovirus expression system of Longacre (1994), since all of these references are interested in using 19 kD C-terminal MSP-1 fragments for the generation of malaria vaccines (FF 8-15). The ordinary artisan would have chosen the baculovirus system for its native processing (FF 6) and high level of expression (FF 7). Such a combination is merely a "predictable use of prior art elements according to their established functions." KSR, 550 U.S. at 417.

Appellants contend that there "is no suggestion in Chappel and Holder to use another leader sequence from a different Plasmodium species or to limit this leader sequence to 32 amino acids. Nor is there any suggestion in this reference to construct a recombinant C-terminal MSP-l protein that has less than 271 amino acids" (App. Br. 11).

We are not persuaded. Longacre (1994) expressly teaches vectors which "were designed to have the P. vivax MSP1 signal sequence which

would be necessary both for secretion and membrane expression" (Longacre (1994) 194, col. 2; FF 16). Longacre (1994) teaches that this results in excellent secretion to obtain enriched preparations of recombinant protein (FF 7).

Regarding the use of a shorter recombinant C-terminal MSP-1 protein, Appellants arguments are not persuasive for two reasons. First, Longacre (1994) and Longacre (1995) both teach the use of the shorter 19 kD protein sequence for expression (see, e.g., FF 9). Second, all of the claims included in this rejection use the open "comprising" transition term. In fact, claims 157 and 158 demonstrate the inclusion of additional sequence of the MSP-1 protein (see Claim 157). In Crish, our reviewing court directly confronted the issue where a subelement of a claim limited the claim, but the claim also began with the open ended transition term "comprising." Crish found that the "reasonable interpretation of the claims containing both of the terms 'comprising' and 'consists' is that the term 'consists' limits the 'said portion' language to the subsequently recited numbered nucleotides, but the earlier term 'comprising' means that the claim can include that portion plus other nucleotides." In re Crish, 393 F.3d 1253, 1257 (Fed. Cir. 2004). Applying Crish to the instant claims, the use of "comprising" is reasonably interpreted as permitting additional sequence in the compositions.

Appellants contend that "Chappel and Holder fail to suggest that their recombinant proteins recited therein have the ability to induce an immune response which can inhibit parasitemia in vivo in a host infected with a Plasmodium parasite. At best their conclusion of their study was speculative" (App. Br. 12).

Kubin stated that "[r]esponding to concerns about uncertainty in the prior art influencing the purported success of the claimed combination, this court [in *O'Farrell*] stated: '[o]bviousness does not require absolute predictability of success … all that is required is a reasonable expectation of success.'" In re Kubin, 561 F.3d 1351, 1360 (Fed. Cir. 2009) (citing In re *O'Farrell*, 853 F.2d 894, 903-904 (Fed. Cir. 1988)).

Here, the teachings of Chappel and Miller support a strong expectation of efficacy. Chappel teaches that "the first EGF-like domain in P. falciparum MSP1 is a target for antibodies capable of inhibiting parasite invasion in vitro" (Chappel 308, col. 2; FF 13). Miller teaches that "[i]mmunization with the first identified Plasmodium falciparum merozoite surface protein (MSP-l) protected monkeys from an otherwise fatal infection" (Miller, abstract; FF 14).

Further, as discussed above, the burden of demonstrating that the prior art combination would not inherently result in a vaccinating composition which inhibits parasitemia in vivo in an infected host rests with Appellants. See In re Best, 562 F.2d 1252, 1255 (CCPA 1977).

Unexpected results

Appellants contend that Arnot describes that "unexpected results of enhanced parasite-specific antibody titers, a larger induction of antibodies and higher levels of growth inhibition were achieved with baculovirus produced MSP-1_{19}" (App. Br. 13).

We are not persuaded for the reasons given above. Specifically, Appellants have not provided a comparison with the closest prior art. See In re Baxter Travenol Labs., 952 F.2d 388, 392 (Fed. Cir. 1991) ("[W]hen

unexpected results are used as evidence of nonobviousness, the results must be shown to be unexpected compared with the closest prior art.").

Conclusions of Law

The evidence of record supports the Examiner's conclusion that Chappel, Miller, Longacre (1995) and Longacre (1994) render obvious the method of claim 151. Appellants have not presented evidence of secondary considerations, that when weighed with the evidence of obviousness, are sufficient to support a conclusion of non-obviousness.

C. and D. 35 U.S.C. § 103(a) over Longacre (1995), Longacre (1994), and Holder and Longacre (1995), Longacre (1994), Chappel, Miller and Holder

The Examiner finds that

> Holder et al. teach the merozoite surface protein (MSP-l) of P. falciparum, or of other malarial parasite species infectious in humans or mice, as a vaccine candidate (see e.g. col. 1-3) and teach recombinant peptides derived from the 19kDa C-terminal fragment of the MSP-l of P. falciparum which comprise the 2 EGF regions of the p 19 protein. The peptides are comprised, in native conformation, in a vaccine administered with an appropriate adjuvant such as alum

(Ans. 11). The Examiner finds it would have been obvious since "the recombinant MSP-l C-terminal polypeptides comprising the EGF-like domains are suggested for use in vaccines and Holder et al. teach the incorporation of MSP-l polypeptides comprising the EGF domains in vaccine compositions comprising alum" (Ans. 11).

Appellants rely upon overcoming the base rejections over Longacre (1995) and Longacre (1994), or Longacre (1995), Longacre (1994), Chappel,

and Miller. Appellants provide no specific arguments why the use of Alum would not have been obvious.

Having already affirmed the base rejections over Longacre (1995) and Longacre (1994), or Longacre (1995), Longacre (1994), Chappel, and Miller, we also agree with the Examiner that substantial evidence supports the Examiner's finding that the incorporation of alum, the "only adjuvant routinely licensed for human use" (Longacre[7] Dec. 11 ¶ 10) and the only adjuvant expressly taught by Holder (see Holder, col. 4, l. 18) would have reasonably been obvious.

SUMMARY

In summary, we affirm the rejection of claim 153, under 35 U.S.C. § 103(a) as obvious over Longacre (1995) and Longacre (1994). Pursuant to 37 C.F.R. § 41.37(c)(1)(vii)(2006), we also affirm the rejection of claims 169, 172, and 175, as these claims were not argued separately.

We affirm the rejection of claim 151 under 35 U.S.C. § 103(a) as obvious over Longacre (1995), Longacre (1994), Chappel, and Miller. Pursuant to 37 C.F.R. § 41.37(c)(1)(vii)(2006), we also affirm the rejection of claims 152, 154, 155, 157, 158, 160, 161, 163, 164, 166, 167, 168, 170, 171, 173, and 174, as these claims were not argued separately.

We affirm the rejection of claims 134, 139-141, 145, 148-150, 176, and 177 under 35 U.S.C. § 103(a) as obvious over Longacre (1995), Longacre (1994), and Holder.

We affirm the rejection of claims 134, 139-142, 148, 150, 176, and

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[7] Declaration of Dr. Shirley Longacre, filed June 16, 2006.

177 under 35 U.S.C. § 103(a) as obvious over Chappel, Miller, Longacre (1995), Longacre (1994), and Holder.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED

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